

age of 2.4 ± 1.4 years and that of group DB was 7.4 ± 6.3 years. The difference in mean ages is the result of group DB including a single donkey aged 13 years. The mean mass of Group D was 144 ± 22.6 kg and that of Group DB was 139 ± 34.6 kg. No statistical difference was found between the ages and weights of the 2 groups using Student's *t*-tests.

The surgeons performing the procedure and selected observers did not know which drug had been administered. All the donkeys were sedated in order to facilitate their castration. Two donkeys were used as part of the pilot trial and were castrated by means of a standard castration procedure as described for equines²⁷. These results of the pilot trial were not included for analysis. In the remaining 10 donkeys the testicular artery was ligated laparoscopically with a Filshie clip as described by Briggs, Gottschalk, Gerber and Joubert (Research Protocol, University of Pretoria, Project No. 36.5.95).

Before commencement of the trial, complete physical examination and blood counts were performed to establish clinical normality. Preoperative serum samples were taken and stored for analysis as required. Food was withdrawn from the donkeys 24 h before the trial and *ad lib* water was allowed until the time of the trial. The animals were kept outdoors in paddocks. The preparation involved the following: an area over the left jugular grooves, the left shoulders, sternum and pectoral muscles was shaved. The jugular groove was surgically prepared. A small bleb of local anaesthetic (Lignocaine 2%, Centaur Laboratories) was placed subcutaneously over the jugular vein and an intravenous Teflon catheter (Intraflo, AME Medical) was inserted into the left jugular vein and sutured in place. This catheter was used for all intravenous drug administrations. The catheter was flushed regularly with heparinised saline to ensure that it remained patent throughout the trial. The donkeys were then led inside and restrained in stocks. Electrocardiograph (ECG) electrodes were placed in a base-apex configuration on the shaved areas of the left shoulder, sternum and pectoral muscles. The ECG electrodes were connected to an ECG monitor (Capnomac II, Datex). The collecting tube from a capnograph (Ultima Capnomac, Datex) was placed into the left ventral meatus.

All data were recorded at the following time intervals: -5, 0, 1, 2, 3, 4, 5, 10, 15, 20 min and then every 10 min thereafter until the procedure was completed, unless specified. Heart rate and rhythm were monitored using the ECG machine.

Rhythm abnormalities were recorded in terms of frequency, type and length of time after administration of the drugs. Respiratory rate and rhythm were monitored physically by chest wall movements and on the capnograph to detect apnoeic periods. Respiratory rhythm abnormalities were recorded. Mucous membrane colour and capillary refill times were monitored and abnormal findings were recorded.

Sedation was characterised by lowering of the head, relaxation of the upper eyelids, drooping of the lower lip and drooping of the ears. The sedation was graded according to a numerical scale: 0 = no sedation; 1 = head normal position, relaxed lower lip and eyelids; 2 = head lowered, drooping eyelids and lip; 3 = head fully lowered, drooping eyelids and lips²⁶. The time to onset of sedation was recorded.

The degree of analgesia was assessed by the response of the animal to a needle-prick applied to the base of the ear, shoulder and fore hoof coronary band at time 0 and thereafter at 5, 10, 15, 20 min and every 10 min thereafter until the end of the procedure^{15,21}. The analgesia was scored according to a numerical rating scale: 0 = no analgesia; 1 = conscious awareness and subdued response; 2 = awareness but no response; 3 = no response to test^{2,6,26}. The use of numerical rating scales for the assessment of pain is a useful tool but the sensitivity of this scale in detecting small differences is limited¹.

Additional doses of detomidine and/or butorphanol at 25–50% of the original dose were given when the degree of sedation or analgesia was considered insufficient. This occurred only in group D. The sedation or analgesia was considered insufficient when the donkeys moved in response to surgical stimuli, were restless in the crush or the sedation or analgesic score was 0–1. Donkeys that received additional doses of either butorphanol or detomidine were given a score of 0 for sedation and analgesia for evaluation purposes from that point onwards.

The time to the end of sedation was recorded. The surgeon performing the procedure and the observers assessed the degree of analgesia and sedation subjectively using the response to surgical stimuli and the ability to complete the procedure with minimum discomfort to the donkey. When additional doses of detomidine and/or butorphanol were required, this was used as the end point of sedation.

Emergency drugs and yohimbine were kept at hand. Animals that developed clinical abnormalities were treated appropriately according to accepted practices. All abnormal clinical findings were noted

and treatments given recorded.

Groups were compared according to weight, age, drug dose and procedure time was done using Student's *t*-tests. For sedative and analgesic times a 2-way analysis of variance was used. The statistical difference was set at 0.05. All data from each group were analysed for means, standard deviations and modes. Heart and respiratory rates were analysed within each group and between groups. The data from times -5 and 0 minutes were pooled when analysed with reference time 0. Sedative and analgesic scores were summed separately for each time interval. The summed values were used for analysis and these were graphed. Histograms were also used to determine the frequency of a particular sedative or analgesic score in each of the 2 groups. Graphs were used to show trends (blood pressure, respiratory rate).

The Research and Ethics committees of the Faculty of Veterinary Science at the University of Pretoria approved this trial (Project Number: 36.5.97).

RESULTS

Drug dosages

Initially Group D received 9.9 ± 1.5 $\mu\text{g}/\text{kg}$ of detomidine while Group DB received 10.1 ± 4.7 $\mu\text{g}/\text{kg}$ of detomidine and 25.2 ± 1.2 $\mu\text{g}/\text{kg}$ of butorphanol. There was no statistical difference between the 2 groups with respect to the initial dose of detomidine given ($P > 0.05$). In Group D, 1 donkey received an additional dose of detomidine (3.4 $\mu\text{g}/\text{kg}$), while 2 donkeys received butorphanol at an average dose of 24.3 ± 2.4 $\mu\text{g}/\text{kg}$. Group DB did not receive additional doses of detomidine or butorphanol for analgesia or sedation. Table 1 summarises the dose and drugs given to each donkey.

Sedation and analgesia

Sedation

The onset of sedation (sedative score ≥ 2) was more rapid in Group DB than in Group D (Table 2), and this was statistically significant ($P < 0.01$). The average length of sedation for Group D was 20 min and that of Group DB was 1 h 7 min (Table 2), which was also statistically significant ($P < 0.01$). A sedative score of 3 was maintained for only 10 min in Group D compared to 40 min in Group DB. Two donkeys in Group D did not achieve a score of 3 while all donkeys in Group DB did. All donkeys in Group D had achieved a score of 1 by 20 min while most of the donkeys in Group DB had a score of 3 for the same time interval. By the end of the procedure, most donkeys

in Group DB had a score of 2, while the Group D donkeys showed no evidence of sedation and had then required additional drugs. Donkeys requiring additional sedation in Group D that were given butorphanol easily obtained a score of 3. In summary, sedation was of shorter duration and intensity in Group D than in Group DB (Fig. 1).

Analgesia

For analgesia tests conducted around the head, Group D produced a mode score of 2 at 5 min, which lasted for 20 min. Group DB produced a mode score of 2 at 5 min and 3 at 10 min. In Group DB a score of 2 or more was maintained for at least 40 min. Similar results were seen for the analgesia tests conduct on the shoulder area. In Group D, coronary band pain was poorly attenuated at all points in time while in Group DB a mode score of 2 was initially achieved. In general, the analgesia lasted twice as long and was of greater intensity in Group DB compared to Group D. The difference between detomidine alone and detomidine-butorphanol are also more apparent graphically as illustrated in Figs 2–4. During the procedure, 3 donkeys from Group D required additional sedation and analgesia, 2 donkeys received butorphanol while 1 donkey received detomidine.

Procedure times

The median times of the procedures performed in Group D and Group DB were of similar length, 45 min 31 sec and 43 min, respectively, and were not statistically different, ($P > 0.05$) (Table 2).

Cardiovascular and respiratory changes

The pre-treatment mean heart rates were 53.3 and 45.3 beats per minute for Group D and Group DB respectively, which dropped to 38.4 and 29.4 in the first minute after treatment for Group D and Group DB. The drop in heart rate was statistically significant and heart rate remained significantly depressed through the entire procedure ($P < 0.05$). There was, however, no statistical difference between the 2 groups at any time. The heart rates are graphically represented in Fig. 5. One donkey in Group D developed an atrioventricular block while another donkey in group DB developed a sinoatrial block.

The respiratory rates tended to decrease in the first few minutes, after which the rate stabilised. There was, however, no statistically significant difference in respiratory rate between the groups. Four donkeys had irregular respiratory patterns.

Table 1: Drug dosages.

Group/ Donkey No.	Detomidine		Butorphanol	
	1st dose ^a	Additional dose ^b	1st dose	Additional dose
Group D				
1	1.70			4.00
8	1.40	0.50		
25	1.20			
31	1.20			3.00
20	1.60			
Group DB				
22	1.20		3.00	
11	1.00		2.20	
3	1.80		4.50	
14	1.60		4.00	
9	2.70		6.80	
Mean	1.54	0.50	4.10	3.50
Mean ($\mu\text{g/kg}$)	10.9	3.4	25.2	12.2

^aDosages are recorded in milligrams given to each donkey at time 0 (1st dose) and the dose of any additional drugs given when sedation or analgesia was insufficient.

^bThe time to the administration of any additional drugs is indicated in Table 2 under the heading 'length of sedation'.

Table 2: Sedation and procedure times (min:sec).

Group D Donkey No.:	1	8	25	31	20	Mean	SD ^a
	Onset of sedation ^b	4:16	4:28	4:50	4:08		
Length of sedation ^c	14:20	21:32	21:12	8:52	36:08	20:25	10:14
Length of procedure ^d	57:31	82:00	18:06	21:19	48:40	45:31	26:34

Group DB Donkey No.:	22	11	3	14	9	Mean	SD
	Onset of sedation	3:38	3:28	3:28	2:56		
Length of sedation	89:16	87:13	59:15	43:54	59:11	67:46	19:44
Length of procedure	42:00	30:12	54:32	39:45	48:30	43:00	9:12

^aSD is the standard deviation for each measurement.

^bOnset of sedation records the time from drug administration to the point when a sedation of score of 2 or more was achieved.

^cLength of sedation gives the time from drug administration until a sedative or analgesic score of less than 2 was achieved.

^dLength of procedure records the duration of the laparoscopic procedure until the last stitch was placed.

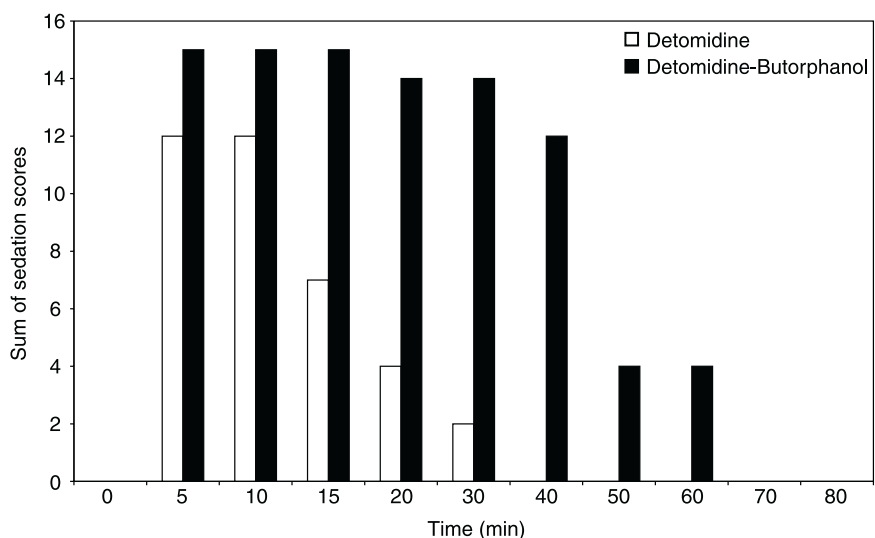


Fig. 1: Sedation score per time interval. The scores for each group were summed. The maximum score for each group in a particular time interval is 15.

Three of these donkeys were from Group DB and the other donkey was from Group D. The irregular respiratory pattern appeared in the Group D donkey only after butorphanol was administered to correct insufficient sedation and analgesia. The respiratory rates for the donkeys are graphically displayed in Fig. 6.

Adverse reactions

Two donkeys from Group D showed pain in response to surgical manipulation. Another 2 from Group D were agitated during the procedure. These problems developed within 10 min of administration of detomidine. One donkey went down in the crush after receiving 20 $\mu\text{g}/\text{kg}$ detomidine and 50 $\mu\text{g}/\text{kg}$ butorphanol. This was an unintentional error due to miscalculation of drug dosages. The results relating to this donkey were not included in the analysis. The donkey was treated with yohimbine (Yohimbine, Centaur Laboratories) (0.25 mg/kg), and replaced with another donkey in the trial. Two donkeys urinated during or shortly after the procedure. Both these donkeys were from Group DB. One donkey from Group DB developed obvious facial muscle twitches. The complications are recorded in Table 3.

DISCUSSION

The recommended dose of detomidine in donkeys is 20 $\mu\text{g}/\text{kg}$ and this provides both analgesia and sedation¹⁹. Lower doses did not produce analgesia¹⁹. Detomidine has been used in doses ranging from 10–20 $\mu\text{g}/\text{kg}$ for clinical sedation and this dose range has been found highly effective in horses^{3,4,6,21}. Higher doses of detomidine have been recommended to increase analgesia and prolong sedation in horses^{4,11}. It has been suggested that donkeys require a higher dose of detomidine for sedation than horses^{9,19,29}.

Butorphanol is 7, 20 and 40 times more potent than morphine, pentazocine and pethidine respectively as an analgesic in laboratory animals^{20,22}. At a dose of 400 $\mu\text{g}/\text{kg}$, butorphanol is capable of relieving superficial pain for 30 min and visceral pain for 90 min in horses^{14,20}. Butorphanol is less effective in increasing visceral pain threshold than xylazine but more effective than morphine, levorphanol and flunixin¹⁴. A dose of less than 50 $\mu\text{g}/\text{kg}$ resulted in poor superficial analgesia but effective visceral analgesia¹⁵. The analgesic effect, duration and depth are dose-related¹³. Doses of more than 220 $\mu\text{g}/\text{kg}$ intravenously are associated with excitation, ataxia and muscle twitches, while doses of 100 $\mu\text{g}/\text{kg}$ produce minimal side-effects^{20,22,23}. High doses of butorphanol will result in an antago-

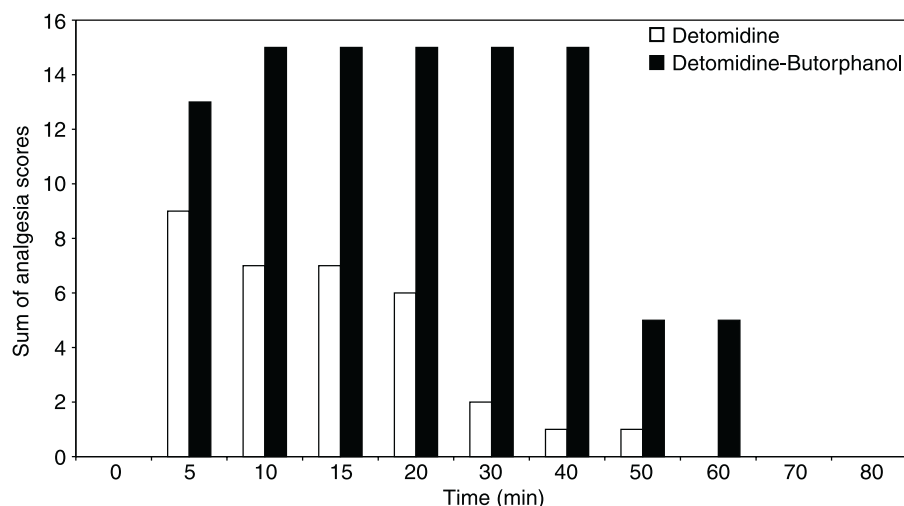


Fig. 2: Analgesia scores for the pain tests conducted around the ears. The scores for each time interval for each group were summed. The maximum score for each group in a particular time interval is 15.

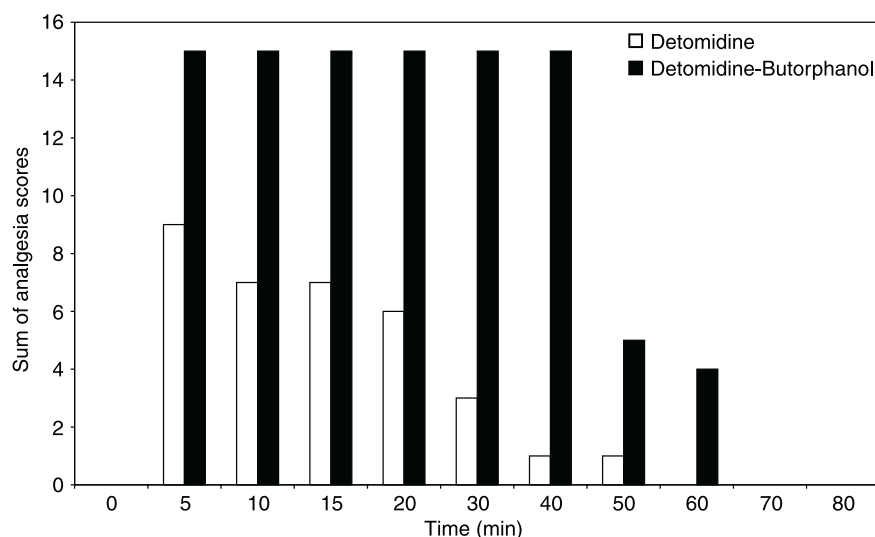


Fig. 3: Analgesia scores for the pain tests conducted on the shoulder. The scores for each time interval for each group were summed. The maximum score for each group in a particular time interval is 15.

Table 3: Adverse reactions.

Adverse reaction ^a	D ^b	DB ^b	Total	Remarks
Sedation inadequate	3*	0	3	
Add butorphanol	2	0	2	
Add detomidine	1	0	1	
Kicking	1	0	1	
AV block	1*	0	1	*After an additional dose of detomidine
SA block	0	1	1	
Erratic respiration	1*	3	4	*After an additional dose of butorphanol
Painful	2	0	2	
Agitated	2	0	2	
Full bladder	0	2	2	
Facial ticks	0	1	1	
Went down	0	1*	1	*Given 20 $\mu\text{g}/\text{kg}$ detomidine and 50 $\mu\text{g}/\text{kg}$ butorphanol inadvertently

^aThe complications are recorded in terms of the number of donkeys developing each type of complication.

^bD = detomidine group; DB = detomidine-butorphanol group.

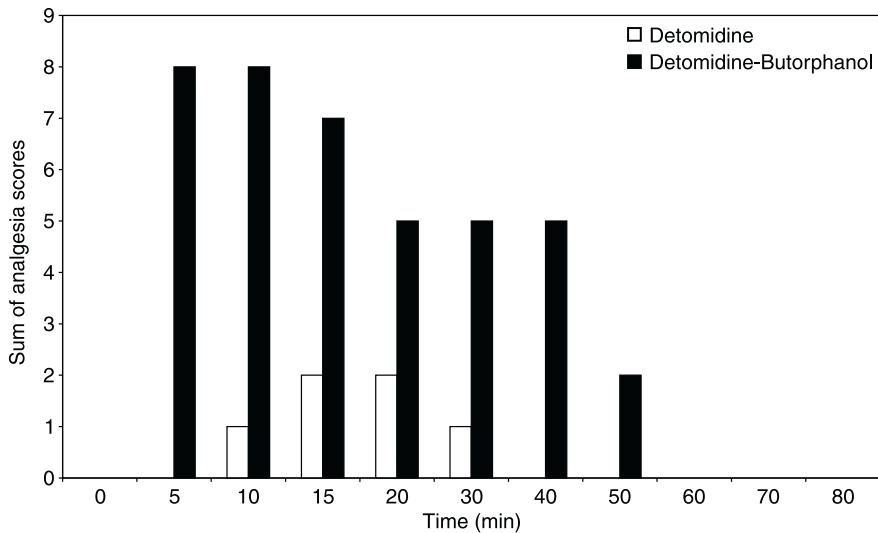


Fig. 4: Analgesia scores for the pain tests conducted on the coronary band. The scores for each time interval for each group were summed. The maximum score for each group in a particular time interval is 15.

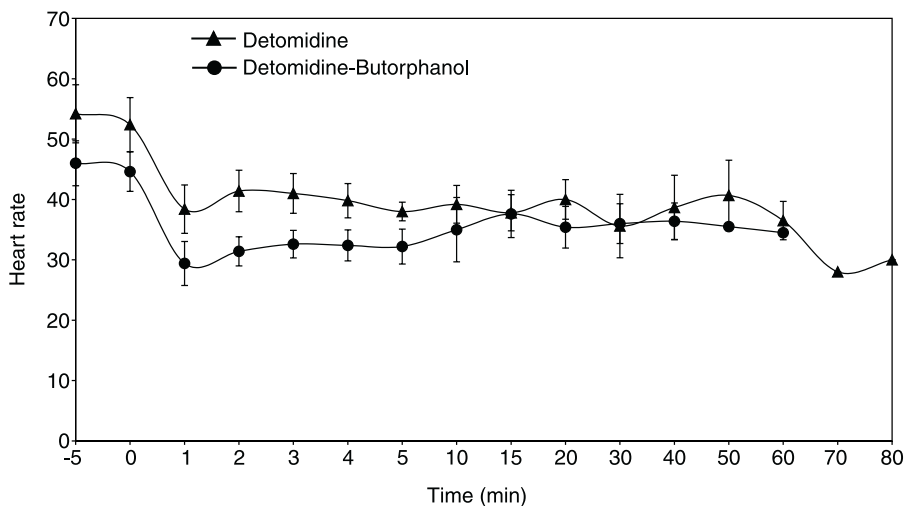


Fig. 5: Mean heart rate for both groups in beats per minute as a function of time. Error bars indicate the standard error of the mean.

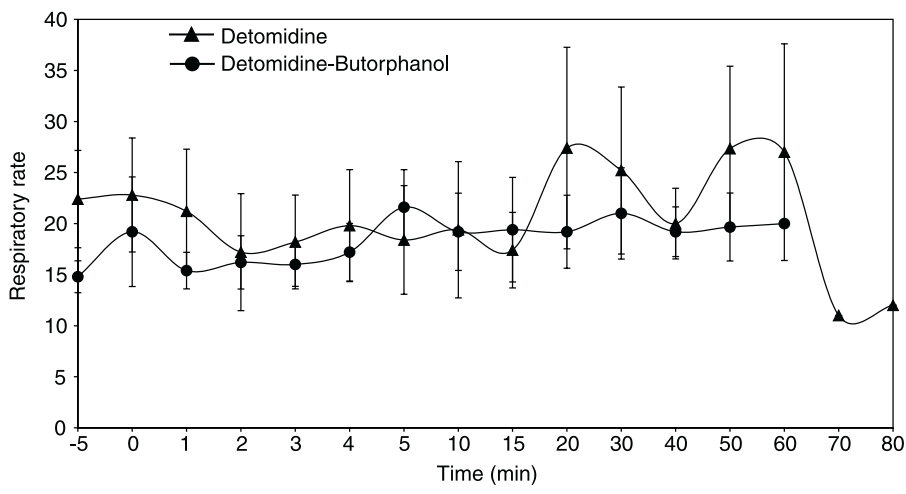


Fig. 6: Mean respiratory rates for both groups in breaths per minute as a function of time. Error bars indicate the standard error of the mean.

nising effect with reversal of analgesia¹⁹. Cardiopulmonary effects are minimal when administered in analgesic doses although butorphanol may induce tachycardia^{15,21,24}. These minimal cardiovascular effects are reflected in studies performed in humans and dogs²⁴. Butorphanol is a potential respiratory depressant but the observed changes in partial pressure of oxygen and carbon dioxide are not statistically significant^{15,23,24,27}. The cardiovascular and respiratory abnormalities are more prominent in pain-free animals²³.

A dose of 10 µg/kg of detomidine in combination with 25–50 µg/kg of butorphanol has been used^{3,17,27} to achieve neuroleptanalgesia. The detomidine can be given 5 min before administration of butorphanol³, or the butorphanol can follow immediately after the detomidine²⁷. Sedation is easily extended by additional doses of either detomidine or butorphanol or both²⁷. Excitation shortly after the administration of this combination has been noted³. Sedation is more profound than if detomidine alone is used, and horses are apparently unaffected by sounds, tactile stimuli and surrounding activity²⁷. Blood pressure effects are minimal after administration of detomidine and butorphanol³. The combination did not significantly alter the arterial partial pressure of carbon dioxide and oxygen^{3,17}. Ataxia is not severe and depends on the dose of detomidine given^{3,27}. It constitutes a potential danger, but most horses appear to 'wake up' and correct their balance before becoming sedated again²⁷. Heart rates drop dramatically after administration of the combination of both drugs²⁷, probably owing to the detomidine component.

Drug dosages

Previous workers have shown that a dose of 10 µg/kg detomidine produced poor analgesia and mild sedation in donkeys²⁰. The donkeys sedated with detomidine alone exhibited a deep pain response at the coronary band. Detomidine cannot be used for moderately to severely painful procedures in donkeys without additional analgesia. It is concluded that detomidine is not as effective an analgesic in the donkey as it is in the horse. The average dose of butorphanol was 28 µg/kg. These doses of detomidine and butorphanol correlate well with dosages recommended for use in equines^{3,17,27}.

Sedation and analgesia

The 2 donkeys used in the pilot trial were cast with the aid of ropes and neutered on the lawn. These 2 donkeys received 20 µg/kg detomidine and 50 µg/kg butorphanol. This procedure

was carried out in order to assess the effect of a higher dose of these drugs. One donkey received detomidine only while the other donkey received both drugs. Neither of these donkeys showed severe ataxia, nor were they easily cast. It was soon evident that the combination of detomidine and butorphanol produced a greater sedative and analgesic effect than detomidine alone. It was surprising that 1 donkey went down in the stocks. Subsequently 7 more donkeys have been castrated using the combination of detomidine and butorphanol at higher doses, and none showed a tendency for recumbence. The donkey went down approximately 4 min after the administration of detomidine (20 µg/kg) and butorphanol (50 µg/kg) in the stocks. This period coincides with the maximum sedative effects of these drugs. The donkey was also being positioned in the crush at the time and it is possible that it slipped and was unable to stand up in the narrow stocks. It was in poor bodily condition, which may have played a role. The remainder of the procedure was performed without additional sedation after the detomidine was partially reversed with yohimbine. No other donkeys went down and the sedation and analgesia proved sufficient at the reduced doses. Detomidine and butorphanol should be used with caution in patients in poor condition.

The donkeys sedated with detomidine only continued to exhibit a deep pain response on the coronary band. They were sedated for approximately 20 min only. A dose of 10 µg/kg of detomidine alone is thus insufficient for standing procedures in the donkey. Other researchers have shown that this dose produced poor analgesia with mild sedation in donkeys²⁰. However, a dose of 10 µg/kg has been shown to be an effective sedative and analgesic in horses^{4,5}.

The failure of detomidine to produce sufficient sedation on its own in the equine has been reported^{3-5,7,8,26}. One donkey in the trial had the ability to kick accurately when stimulated with painful stimuli under detomidine sedation alone. The reaction of a single donkey is of limited value but this should be borne in mind when using this drug on its own. Early in this trial it became evident that the combination of detomidine and butorphanol produced better analgesia and sedation than detomidine alone. The pain and analgesia scores support this hypothesis. For this reason, later in the trial butorphanol was given when the detomidine alone failed. Detomidine and butorphanol used at a dose of 10 µg/kg and 25 µg/kg, respectively, constitute an

effective combination for standing procedures, allowing 60 min of sedation and providing analgesia. The superior sedation is the result of synergistic effects between detomidine and butorphanol.

The average length of sedation with detomidine alone was 20 ± 10 min. This is of shorter duration than reported for donkeys (35 ± 4.01 min)²⁰. The average length of sedation provided by the combination of detomidine and butorphanol was 67 ± 19 min. This correlates with what has been reported for equines^{4,5}.

Cardiovascular changes

After intravenous injection of alpha₂ adrenergic agonists, the following cardiovascular effects have been described. Blood pressure initially increases rapidly due to direct stimulation of peripheral alpha₁ receptors^{3-5,26}, which increases systemic vascular resistance, usually within 2–5 minutes of administration^{3-5,25,26}. This is accompanied by a significant fall in heart rate due to a baroreceptor response^{3-5,25,26}. The duration of bradycardia is unpredictable^{4,20}. After the hypertension, there is a centrally mediated drop in systemic vascular resistance and sympathetic tone, and more prolonged mild hypotension ensues^{3-5,25}. The heart rate usually returns to normal within a few minutes^{5,26}. The cardiovascular side-effects are dose-dependent and reach their maximum effect 15–30 min after intravenous injection⁵. Central venous pressure and pulmonary capillary wedge pressure are not altered by detomidine in horses²⁵. Cardiac output and tissue perfusion are reduced, although no clinical problems due to low tissue perfusion have been reported^{4,5,20,25}.

Heart rates decreased significantly over the first minute. This correlates well with what has been reported in equines treated with detomidine with or without butorphanol, and with the single account of the use of detomidine in donkeys^{4,5,7,8,20,26}. This should coincide with the maximum increase in blood pressure associated with the direct stimulation of peripheral alpha₁ receptors^{3-5,26}. After the initial drop, the heart rate tended to return to baseline values. It is well-known that after administration of alpha₂ adrenergic agonists the heart rate tends to return to normal, usually within 20–30 min. The donkeys were not acclimatised to the crush, as this would have defeated the object of assessing the combination of drugs under field conditions. The stress of the new environment and handling of the animals during preparation may have increased the baseline heart rates owing to an increase in sympathetic tone. The observations of both an

atrioventricular and a sino-atrial block have been reported in the equine following the administration of these drugs³⁻⁵. Both these arrhythmias are well described after the use of alpha₂ adrenergic agonists and result from a decrease in sympathetic tone and an increase in parasympathetic tone.

Respiratory changes

The Cheyne-Stokes respiratory pattern was recognised with the aid of a capnography. The capnograph has been used to evaluate respiratory patterns with the sampling line in the ventral meatus of small animals¹⁹. The Cheyne-Stokes respiratory pattern is the result of altered functioning of the respiratory centres in the brain¹¹. Hypoventilation results in a rise in the arterial partial pressure of carbon dioxide. The chemoreceptors detect the increased partial pressure of carbon dioxide in the arterial blood, and relay the information to the central nervous system to increase ventilation. Hyperventilation over-compensates for raised carbon dioxide levels, and the arterial partial pressure of carbon dioxide drops below normal. The chemoreceptors stop responding and apnoea follows¹¹. Possible mechanisms include altered blood flow, damage to peripheral chemoreceptors and central nervous system damage. Opioids have been reported to cause Cheyne-Stokes respiratory pattern⁶.

Opioids and alpha₂ adrenergic agonists are known to depress ventilation and alter arterial partial pressures of carbon dioxide and oxygen. None of the donkeys showed any symptoms of intra- or post-operative hypoxia or respiratory failure. The possibility of hypoxia has been noted in equines but has never been found to be clinically significant. Blood-gas analysis was not performed. We could find no report of a Cheyne-Stokes respiratory pattern in horses in relation to detomidine and/or butorphanol. The technique of insertion of the capnograph into the ventral meatus has not been evaluated as an experimental tool, but the use of tubing placed into the trachea has been evaluated¹⁹. The difference in respiratory gas composition between the ventral meatus of a nostril and the upper part of the trachea should be negligible. The nasal passageways humidify the air and it is possible that the inspired gases would not be completely humidified when analysed by the capnograph on inspiration. When the individual readings of respiratory rate are analysed for each donkey, the respiratory rate was very erratic between readings. In view of this, it is difficult to find a statistical difference in the respiratory rates, which explains

the irregular nature of the respiratory graph.

Relaxation of the laryngeal and nasal alar muscles owing to detomidine predisposes horses to upper airway obstruction and stridor⁵. This reduction in airway diameter has not been associated with any clinical symptoms but it may cause arterial hypoxaemia⁵.

Adverse reactions

The diuresis induced by detomidine is associated with increased glomerular filtration rates, inhibition of anti-diuretic hormone release, inhibition of anti-diuretic hormone effect on the renal tubules and increased release of atrial natriuretic factor^{5,7}. Two of the donkeys did void their bladders during or shortly after the procedure. This should be borne in mind, especially when urogenital operations are planned. The mechanisms responsible for this are similar to those described for alpha₂ adrenergic agonists.

CONCLUSION

Detomidine alone, at a dose of 10 µg/kg, should not be used without additional analgesia for moderate or severely painful procedures in donkeys. A dose of 10 µg/kg of detomidine with 25 µg/kg of butorphanol was found effective for standing procedures with minimal clinical side-effects. Sedation and analgesia are expected to last approximately 60 minutes.

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